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(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Preservative-Free Multi-Dose Vincristine Solution

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Abstract of the Invention

The invention is directed to a sterile, stable, multiple-dose pharmaceutical product for intravenous use consisting essentially of a non-preserved, ready-to-use solution of a salt of vincristine wherein the concentration of said vincristine in said solution is from about 0.50 mg/mL to about 2.0 mg/mL; wherein the pH of said solution is from about 5.5; and wherein said solution is contained in a multiple-dose unit container.

PRESERVATIVE-FREE MULTIDOSE VINCRISTINE SOLUTION

Background of the Invention

Vincristine, usually in the form of its sulfate salt is a cytotoxic agent active against a variety of hematologic malignancies and solid tumors. Vincristine is an an alkaloid obtained from a common flowering herb, the periwinkle plant (Vincarosia rosea Linn.).

The primary mechanism of action of vincristine in malignant cells is thought to be the arrest of cellular division during metaphase. It is effective against acute leukemia or, together with other antineoplastic agents, against Hodgkins disease, lymphosarcoma, reticulum-cell sarcoma, rhabdomyo sarcoma, neuroblastoma, and Wilm's tumor.

Vincristine is commercially available from several sources as both a preserved and a nonpreserved, ready-to-use, injectable formulation. For example, a vincristine sulfate injection is commercially available from Adria Laboratories Division of Erbamont Inc., under the trade name VINCASAR PFSO as 1 mL and 2 mL single-dose vials. The preserved injectable formulation of vincristine sulfate (1mg/1mL) is available from Eli Lilly under the trade name ONCOVINO in 1 mL, 2 mL and 5 mL multiple-dose vials.

The preserved, ready-to-use injectable formulations of vincristine sulfate are available in multidose forms. The multidose preservative containing formulations are disclosed in U.S. Patent No. 4,619,935, assigned to Eli Lilly. Because of the presence of the preservative agent, typically a paraben, the vial containing the solution may be penetrated multiple times without contamination of the vial contents. Despite the increased shelf life of the formulation, the presence of the preservative, as is acknowledged by the inventors of U.S. Patent No. 4,619,935,

has a deleterious effect upon potency, clarity and pharmaceutical elegance of the formulation.

Accordingly, there exists a need in the art for a multiple-dose formulation of vincristine which is stable and does not contain deleterious effects caused by the presence of preservatives.

The present invention is directed to a sterile, multiple-dose, stable, preservative-free vial of vincristine sulfate solution.

Summary of the Invention

The invention is directed to a sterile, stable, multiple-dose pharmaceutical product for intravenous use consisting essentially of a nonpreserved, ready-to-use solution of a salt of vincristine wherein the concentration of said vincristine in said solution is from about 0.50 mg/mL to about 2.0 mg/mL; wherein the pH of said solution is from about 3.5 to about 5.5; and wherein said solution is contained in a multiple-dose unit container.

The invention is also directed to a method for administering intravenously a multiple number of dosages of a solution of a salt of vincristine. The method includes the steps of:

(a) filling a hypodermic syringe with a measured dosage from a multiple-dose container containing a nonpreserved, ready-to-use solution consisting essentially of a salt of vincristine wherein the concentration of vincristine in said solution is from about 0.50 mg/mL to about 2.0 mg/mL; and wherein the pH of said solution is from about 3.5 to about 5.5;

(b) injecting said dosage intravenously into a patient in need of treatment; and

(c) repeating steps (a) and (b); wherein said dosage is filled from said multiple-dose container.

Detailed Description of the Invention

The invention is directed to a sterile, stable, multiple-dose pharmaceutical product for intravenous use consisting essentially of a nonpreserved, ready-to-use solution of a salt of vincristine wherein the concentration of said vincristine in said solution is from about 0.50 mg/mL to about 2.0 mg/mL; wherein the pH of said solution is from about 3.5 to about 5.5; and wherein said solution is contained in a multiple-dose container.

As used herein the term "multiple-dose container" refers to a multiple-unit container for articles intended for parenteral administration only, and more particularly, the non-preservative containing vincristine salt solution. A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality or purity of the remaining portion. United States Pharmacopeia, 21st Revision, p. 8, 1984 ("USP XXI").

The multiple-dose container, including the closure for the parenteral solution does not interact physically or chemically with the solution in any manner to alter the strength, quality or purity of the solution. The container is preferably made of a material that permits inspection of the interior contents of the container. Preferably the container is made of glass. USP XXI, p. 1138.

In practice, the container preferably takes the form of a glass vial. The vial may be colorless or colored. Examples of colored glass vials suitable for housing vincristine salt solutions include amber type 1 acid treated vials.

The container should be closed by application of a suitable closure in such a manner as to prevent contamination or loss of contents. Closures for multiple-

dose containers should permit the withdrawal of the contents without removal or destruction of the closure. The closure permits penetration by a needle, and, upon withdrawal of the needle, at once recloses the container against contamination. Examples of suitable closures include, but are not limited to, Teflon-faced gray-butyl stoppers or Stelmi 632 stoppers.

The solution inside the multiple-dose container is sterile and stable. As used herein, the term "sterile" refers to a solution which passes the test for sterility set forth in USP XXI, <71>, p. 1156, and the Bacterial Endotoxin Test set forth in USP XXI, <85>, pp. 1165-1167.

As used herein, the term "stable" refers to "shelf stability" of the product upon storage for extended periods. The multiple-dose product of the present invention is stable upon storage under refrigeration at 5°C for periods of up to 18, and perhaps even 24 months. That is, the product does not chemically degrade and thus, lose its potency upon storage for extended periods.

The active pharmaceutical agent in the product of the invention is a pharmaceutically acceptable salt of vincristine. Preferred for use herein is the sulfate salt. Salts other than the sulfate, such as the phosphate salt, may be utilized in the stable solutions of this invention although the sulfate salts are preferred.

Vincristine is present in the product of the invention at from about 0.5 mg to about 2.0 mg per mL of solution, preferably about 0.75 to about 1.5 mg per mL of solution and more preferably at about 1 mg/mL of solution.

The vincristine solution may contain minor amounts of pharmaceutically acceptable excipients as, for example, sugars or polyols derived from sugars, e.g., lactose or mannitol, and agents to buffer the pH as, for example, acetic acid and sodium acetate, sodium hydroxide and

hydrochloric acid. The sugars or polyols derived from sugars are usually present in the formulation from about 10-100 mg/mL. The buffer system should maintain the pH in the range of 3.5 to 5.5 and more preferably from about 4.0 to about 4.5. In the case where an acetate buffer system is used, the molar ratio of acetate to vincristine salt is preferably about 20 to 1 or less. The buffer system further functions to prevent any pH change of the solution due to leaching from the glass or closure of the container.

The vincristine salt solution maintained in the multiple-dose containers does not contain preservatives to provide an increased shelf-life. Rather, the inventors have surprisingly discovered that the ready-to-use solution, particularly if refrigerated, maintains a relatively long shelf-life without a significant reduction in efficacy. This is a key advantage over ready-to-use multiple-dose vincristine salt formulations containing preservatives as the preservatives tend to have a deleterious effect upon potency, clarity, and pharmaceutical elegance.

The product of the invention is prepared according to conventional procedures well known to those in the pharmaceutical arts. Once the vincristine salt solution is prepared, filled into the multiple-dose container, and sealed by inserting a closure to close the container, the solution is ready for patient use. To use the solution, a needle connected to a hypodermic syringe is inserted through the closure, for example a rubber stopper, and the plunger of the syringe is withdrawn a designated length until a measured dosage of the vincristine salt solution is maintained in the syringe. The needle is then withdrawn from the container and the closure automatically reseals to prevent environmental contamination of the vincristine salt solution. The needle is then inserted intravenously into a patient in need of treatment to administer the vincristine

salt solution to the patient.

After this procedure has been performed, there should be a significant amount of vincristine salt solution still contained within the container. To utilize the remaining contents, the above procedure is repeated, that is, the needle of hypodermic syringe/needle assembly is inserted through the closure and into the container, the plunger of the syringe is withdrawn a designated length to produce a measured dosage, the needle is removed from the container closure, and the vincristine salt solution is intravenously administered to a patient.

The above procedure may be utilized for administering multiple doses of vincristine salt solution to the same patient over a period of time or, in the case where the multiple-dose container of the present invention is used in a cancer treatment clinic, to multiple patients. In the later situation, because the concentration of the vincristine salt solution required for treatment may vary from patient to patient, the amount of vincristine salt solution to be administered to each patient may be easily controlled by monitoring the amount of solution withdrawn into the syringe. It is particularly preferred to utilize highly calibrated syringes or syringes of a pre-determined volume to ensure a proper dosage for each patient.

The following examples provide detailed embodiments of the invention and are illustrative in nature.

Example 1

A sterile vincristine sulfate solution having the formulation listed below was prepared and filled into multiple-dose 5 mL glass vials and sealed and stoppered according to procedures for aseptic preparation and fill described in USP XXI.

		Per 5 mL*	Per 10L Batch
1)	Vincristine Sulfate, USP	5.00 mg	10.0 g
2)	Mannitol, USP	500 mg	1000 g
3)	Acetic Acid (0.2M)	0.1275 mL**	255 mL**
4)	Sodium Acetate (0.2M)	0.1225 mL**	245 mL**
5)	Argon	Used as an inert atmosphere during processing.	
6)	Water for Injection, USP qs, ad	5.0 mL	10L

* Excipient amounts are calculated based on the 10L batch.

** Additional quantities may be used for pH adjustment.

Example 2

To determine if the non-preserved multiple-dose product of the present invention could withstand microbiological challenge in accordance with the USP Antimicrobial Preservatives-Effectiveness Test set forth in USP XXI, <51>, p. 1151, the vials prepared as described in Example 1 were placed in a laminar flow hood and the crimp seals used to attach the stoppers to the vials were aseptically removed. Aliquots of the USP specified strains of organisms listed below were added to the vials using an Eppendorf-type pipet. The culture media (soybean-casein digest auger medium including 0.1% Polysorbate-80 according to USP XXI, p. 1152) employed for the test procedures were checked for sterility and capability to allow adequate microbiological growth prior to addition to the multiple-dose vials. The final ratio of organism to product was equivalent to 0.1 mL:20 mL. All samples were taken from the

vials by using sterile syringes equipped with hypodermic needles which were inserted through the stoppers to enable withdrawal of the organism containing solution. Samples were taken at days 0, 7, 14, 21 and 28. (This means that multiple penetrations of the rubber stoppers occurred over the 28-day testing period).

Tests were conducted on a sample containing 5 mg vincristine salt solution/5 mL and on two samples containing 2 mg vincristine salt solution/2 mL. The results for the 5 mg/5 mL sample are shown in Table 1. The results on the 2 samples of the 2 mg/2 mL product are shown in Tables 2 and 3.

Table 1

Results of USP Antimicrobial Preservatives Effectiveness Test

Vincristine Sulfate Solution 5 mg/5 mL

Organism / Time (days)	E. coli cfu/mL	S. aureus cfu/mL	Ps. aeruginosa cfu/mL	C. albicans cfu/mL	A. niger cfu/mL
0	9×10^5	9×10^5	8×10^5	6×10^5	7×10^5
7	<10	50	35	7×10^2	7×10^5
14	<10	<10	<10	25	6×10^5
21	<10	<10	<10	<10	2×10^5
28	<10	<10	<10	<10	5×10^5

Table 2

Results of USP Antimicrobial Preservatives Effectiveness Test

Vincristine Sulfate Solution 2 mg/2 mL

Organism Time (days)	E. coli cfu/mL	S. aureus cfu/mL	Ps. aeruginosa cfu/mL	C. albicans cfu/mL	A. niger cfu/mL
0	1×10^6	3×10^5	5×10^5	2×10^5	1×10^5
7	<100	<100	<100	2×10^3	500
14	<10	<10	<10	<10	<10
21	<10	<10	<10	<10	<10
28	<10	<10	<10	<10	<10

Table 3

Results of USP Antimicrobial Preservatives Effectiveness Test

Vincristine Sulfate Solution 2 mg/2 mL

Organism Time (days)	E. coli cfu/mL	S. aureus cfu/mL	Ps. aeruginosa cfu/mL	C. albicans cfu/mL	A. niger cfu/mL
0	2×10^5	2×10^5	2×10^6	1×10^5	1×10^5
7	<10	<100	6×10^3	8×10^2	1×10^3
14	<10	<10	<10	1×10^3	2×10^3
21	<10	<10	<10	4×10^2	1×10^3
28	<10	<10	<10	2×10^2	1×10^3

As shown by the data in Tables 1-3, the solutions contained in the multiple-dose vials passed the USP Antimicrobial Preservatives-Effectiveness Test over the entire 28 day period without the addition of any preservatives.

Example 3

Three vials containing 5 mg/5 mL of vincristine salt solution were prepared as described in Example 1 and were used in a 24 hour study and a 7 day study to determine their suitability for use as a multiple-dose pharmaceutical product. In the 24-hour study, 1.0 mL of solution was drawn by a needle through the stopper closing the vial at 0, 2, 4, 6 and 24 hour intervals. The test vials were stored both at room temperature and at refrigerated temperatures (5°C) prior to withdrawal of each sample. The potency and purity of each sample were determined and the pH was measured. Table 4 shows the results. Similarly, a longer study of 0, 1, 2, 4 and 7 days was identically performed to that described above. The results are shown in Table 5.

Table 4

	Potency Percent of Initial							
	Room Temperature				Refrigerated			
Hours	I	II	III	Avg	I	II	III	Avg
0	100	100	100	100	100	100	100	100
2	100	102	99	100	100	98	99	99
4	101	101	99	100	101	100	99	100
6	100	101	100	100	99	--*	99	99
24	100	101	98	100	97	98	98	98

* Instrument error

	Degradation Products %							
0	2.3	2.3	2.4	2.3	2.8	2.8	2.8	2.8
2	2.4	2.5	3.1	2.7	3.0	2.8	3.0	2.9
4	2.5	2.6	2.7	2.6	3.2	3.3	3.7	3.4
6	2.6	2.3	2.9	2.6	3.1	3.8	3.1	3.3
24	2.6	2.8	3.3.	2.9	3.2	3.2	3.4	3.3

	pH							
0	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
6	4.4	4.4	4.4	4.4	4.5	4.5	4.5	4.5
24	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4

Table 5

Day	Potency Percent of Initial							
	Room Temperature				Refrigerated			
	I	II	III	Avg	I	II	III	Avg
0	100	100	100	100	100	100	100	100
1	99	100	101	100	100	101	99	100
2	99	100	100	100	99	96	99	98
4	98	99	99	99	99	95	97	97
7	98	99	97	98	98	96	98	97
	Degradation Products %							
0	2.4	2.5	2.6	2.5	2.6	2.8	3.4	2.9
1	2.4	2.5	2.5	2.5	2.9	2.9	2.9	2.9
2	3.0	2.9	3.0	3.0	3.0	4.0	3.0	3.3
4	3.1	3.2	3.2	3.2	3.2	3.2	3.2	3.2
7	3.5	3.4	3.5	3.5	3.4	3.7	3.4	3.5
	pH							
0	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
1	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
2	4.3	4.3	4.3	4.3	4.3	4.3	4.4	4.3
4	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3
7	4.3	4.3	4.3	4.3	4.3	4.3	4.3	4.3

As shown by the results in Tables 4 and 5, the multiple-dose product of the present invention can withstand multiple entries of the container without effecting the strength, purity and quality of the vincristine sulfate (5 mg/5 mL) active drug substance. As such, it is suitable for use as a multiple-dose pharmaceutical product.

Having described the invention in detail and by reference to preferred embodiments thereof, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims.

What is claimed is:

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A sterile, stable, multidose pharmaceutical product for parenteral use consisting essentially of a nonpreserved, ready-to-use solution of a salt of vincristine wherein the concentration of vincristine in said solution is from about 0.50 mg/mL to about 2.0 mg/mL; wherein the pH of said solution is from about 3.5 to about 5.5; and wherein said solution is contained in a multiple-dose unit container.

2. A product according to claim 1 wherein said salt of vincristine is the sulfate salt.

3. A product according to claim 2 wherein said solution is administered intravenously.

4. A product according to claim 3 wherein the concentration of said vincristine in said solution is about 1.0 mg/mL.

5. A product according to claim 4 wherein the pH of said solution is from about 4.0 to about 4.5.

6. A product according to claim 3 wherein said solution further contains amounts of pharmaceutically acceptable excipients.

7. A product according to claim 6 wherein said pharmaceutically acceptable excipients comprise sugars or alcohols derived from sugars.

8. A product according to claim 6 wherein said product additionally includes pH buffers.

9. A product according to claim 8 wherein said pH buffers comprise an acetic acid-sodium acetate buffer system.

10. A sterile, stable, multidose pharmaceutical product for parenteral use consisting essentially of a non-preserved, ready-to-use solution of a salt of vincristine wherein the concentration of vincristine in said solution is from about 0.50 mg/mL to about 2.0 mg/mL;

a pharmaceutically acceptable excipient comprising a sugar or an alcohol derived from sugars; and

a pH buffer system;

wherein the pH of said solution is from about 4.0 to about 4.5; and wherein said solution is contained in a multiple-dose unit container

11. The product according to claim 10 wherein said salt of vincristine is the sulfate salt.

12. The product according to claim 11 wherein the concentration of said vincristine in said solution is about 1.0 mg/mL.

13. A method for administering intravenously a multiple number of dosages of a solution of a salt of vincristine comprising the steps of:

(a) filing a hypodermic syringe with a measured dosage from a multiple-dose container containing a nonpreserved, ready-to-use solution consisting essentially of a salt of vincristine wherein the concentration of vincristine in said solution is from about 0.50 mg/mL to about 2.0 mg/mL; and wherein the pH of said solution is from about 3.5 to about 5.5;

(b) injecting said dosage intravenously into a patient in need of treatment; and

(c) repeating steps (a) and (b); wherein said dosage is filled from said multiple-dose container.

14. A method according to claim 13 wherein said salt of vincristine is the sulfate salt.

15. A method according to claim 14 wherein said solution further contains amounts of pharmaceutically acceptable excipients.

16. A method according to claim 15 wherein said pharmaceutically acceptable excipients comprise sugars or alcohols derived from sugars.

17. A method according to claim 15 wherein said product additionally includes pH buffers.

18. A method according to claim 17 wherein said pH buffers comprise an acetic acid-sodium acetate buffer system.

19. A method according to claim 14 wherein the concentration of said vincristine in said solution is about 1.0 mg/mL.

20. A method according to claim 14 wherein said multiple number of dosages are administered to different patients.